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Serum Vitamin D Level among Infertile Women at Basra City

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Abstract

Objective: The objective is to assess Serum Vitamin D level among infertile women in comparison to fertile women and study the possible factors that could lead to its depletion in spite of abundant sunlight in Basra city.

Methods: This is a prospective case control study was conducted at Basra infertility center and outpatient Department at Basra Maternity hospital during the period from (15th September, 2017 to 5th March, 2018). Group I include 106 infertile women and group II 104 fertile women. In both groups women were randomly selected and were consented to participate in the study. In both groups women were assessed by specific questionnaire and Serum Vitamin D level was measured by ELISA test. In this research, the normal level for Vitamin D was considered to be greater than or equal to 20 ng/mL and serum level lower than 20 ng/mL was considered to be the deficit level.

Results: Among the 106 studied women, 81 (76.4%) of them had Vitamin D deficiency and 25 (23.6%) of them had normal level of vitamin D. The lowest level of vitamin D in studied women was 0.3 ng/mL and the highest level of that was 62 ng/mL with p-value 0.000. Many factors have statistically significant effect on serum level of Vitamin D like socio-economic status with p-value=0.000, dietary habit with p-value=0.003, occupation with p-value=0.019, exposure to sun light with p-value=0.002, while other factors have no statistically significant effect like age of infertile women with p-value=0.05, BMI with p-value=0.101, race with p-value=0.5, level of education 0.243, type of clothes with p-value=0.11, color of clothes with p-value=0.1.

Conclusion: In spite of abundant sun in our locality (Basra city) where this study was conducted, serum vitamin D levels were lower among infertile women compare to the fertile women. According to the conclusion of many researches worldwide about the association of vitamin D deficiency and infertility, Vitamin D deficiency should be kept in mind in the management of infertile women at our city. Among the etiological factors (socio-economic status, occupation and exposure to sun light, dietary habit) were found to be significant.

Keywords: Serum vitamin D; Infertility; Hyperparathyroidism; Anti-epileptic; Radiotherapy

Introduction

Infertility is defined by the International Committee for Monitoring is failure to achieve a pregnancy after one year or more of regular unprotected sexual intercourse [1]. According to the World Health Organization, about 10%-25% of the couples complain from infertility disorder. It affects approximately 60-80 million couples worldwide. Infertility in females might result from many causes including the deficiency of vitamin D [2,3]. It has been reported that in about 35% of cases of infertility is due to a female factor, in 30% to a male factor, in 20% to abnormalities discovered in both partners, and in 15% of cases no causes can be made after a full investigation [4]. Vitamin D is likely one of the oldest hormones, having existed for beyond 750 million years [5].

Based on previously defined serum criteria (25-OH-D level >30 ng/mL was defined to reflect “replete” vitamin D status; level between 20-30 ng/mL was taken to reflect vitamin D insufficiency. Whereas, 25-OH-D level <20 ng/mL defined evidence of vitamin D deficiency [6]. Normal daily requirement of Vitamin D in teens (14-18 years) is 600 IU and for adults (19-70 years) is 600 IU (Conversion: 1 µg=40 IU and 0.025 µg=1 IU) [7,8]. Vitamin D receptor has been identified in the ovary (particularly granulose cells), uterus, placenta, testis, hypothalamus and pituitary gland. Up to date, it has been suggested that vitamin D and its active metabolite 1,25-(OH)2D3 play a major role in reproductive physiology [9,10].

At the level of the ovaries; 1,25-(OH)2D3 stimulates the production of progesterone, estradiol and estrogen by 13%,9% and 21% respectively [2]. Among women, vitamin D has been reported to regulate the concentration of Anti-Mullerian Hormone (AMH) in serum [11]. The role of vitamin D on ovarian granuloma cells responsible for steroid genesis was established after finding 1-α-hydroxylase and VDR receptors in deciduae, placentas, ovaries, endometrium, pituitary glands, human testis, sperm, epididymis, seminal vesicle, prostate, cervix, breast tissue and hypothalamus [9]. At the level of the uterus; Vitamin D effect on endometrial receptivity by up-regulating HOXA10 in endometrial stromal cells. HOXA10 is a home box-containing transcription factor that is important for endometrial receptivity and decidualization [12].

Vitamin D insufficiency or deficiency is present in between 58%-91% of women with infertility [9]. Multiple factors such as age, skin pigmentation, women clothing, physical activity, obesity, receiving nutrients, sunlight (ultra-violate radiation between 290-315 nm) and seasonal changes could have an impact on the blood vitamin D level

[13]. Sun exposure time varies depending on skin color and sensitivity areas of skin exposed (arms and leg recommended), time of day and altitude all have direct effect on serum Vitamin D. Sunscreen use of SPF15 can decease Vitamin D3 synthesis by 99% [3].

Medical disorders like mal absorption (Crohn's disease, celiac disease, cystic fibrosis), liver disease, renal disease, nephritic syndrome, hyperparathyroidism, chronic granulomatous disease all limited Vitamin D uptake or synthesis [14]. Medications such as anti-convulsants, glucocorticoids, rifampcin, anti-fungal and highly active anti-retroviral treatment all reduce Vitamin D absorption. Active malignant disease and exposure to chemotherapy or radiotherapy [15] bariatric surgery [16], several analyses highlighted that vitamin D deficiency increased among smokers compared to non-smokers [17].

Aim of the study is to know the distribution of low serum vitamin D level among infertile women at Basra city and the possible etiological factors.

Patients and Methods

This is a prospective case control study was carried out at Basra Infertility Center in Basra Hospital for Maternity and Children during the period (15th September, 2017 to 5th March, 2018).

It included 106 women with un-ovulatory or unexplained infertility (study group), their ages ranged from 18-45 years and 104 apparently fertile women of the same age group (control group) which consist of healthy women with one or more successful pregnancy without any obstetrical or medical problems attending the gynecological outpatient Department in Basra Hospital for Maternity and Children for different gynecological problems.

A special questionnaire was designed for the purpose of the study and included the following information; name. According to age women are divided into three groups(15-20 years, 21-40 years, 41-45 years), Occupation (house hold or outdoor activity). Type of infertility either primary or secondary and its duration, presence of polycystic ovaries women or not (according to Rotterdam criteria) [18]. Body mass index was calculated as weight in kg/height in m^2 and the women were categorized as (slim BMI <19.9, normal weigh BMI 20.0-25.0, over weight BMI 25.1-29.9, obese BMI >30). Socio-economic status (family income was classified into four subgroups; <400000 Dinar (ID)/month (low socio-economic class) 400000-799000 Dinar (ID)/ month (mid socio-economic class), 800000-1999000 or equal to 2000000 Iraqi Dinar (ID)/month (high socio-economic). Dietary intake either Vitamin D rich diet (fish, egg yolk, meat, milk, cereals and fortified beverages) or poor diet. Race (Negro or white). Exposure to sunlight (measured by min) about 5 to 30 min for two to three times/ week without use of sun screen consider as a good exposure and less than this periods of exposure or use of sunscreen consider as poor exposure. Types of clothing (used of abaya, hijab or boshiya). Color of clothing (black or multiple colors). Drugs history like the use of anti-epileptic, glucocorticoid or HIV medications). Level of education (illiterate, primary or secondary school and high education), also we asked about the tobacco smoking.

Written consent was initially signed by infertile and fertile women to participate in the study after explaining the method for them and the demographic data were collected by questionnaire.

All the participants (control and case) were randomly selected by alternate day method according to their attendance to the infertility and outpatient department.

Inclusion criteria include age (15-45 years), Women with unovulatory or unexplained type of infertility, Normal hormonal level of (FSH, LH, Prolactin and TSH). Regarding control group, women under study should deliver at least one baby without history of primary or secondary infertility.

Exclusion criteria include patients with tubal factor infertility or has uterine anomalies or pathology that resulted in infertility, patients with galactorrhoea (Elevated prolactin level), couples with male factor infertility (abnormal seminal fluid analysis), women with underlying medical condition such as heart, liver and kidney disease, female use drugs that interfere with the metabolism of Vitamin D, women aged above 45 years, less than 18 years.

In both groups serum level of serum Vitamin D was detected spectrophotometrically at 254 nm.

Analysis of the data was done using the Statistical Packages for Social Science (SPSS) version 24. Data were presented as numbers and percentages for non-parametric variables and mean ± SD for parametric variables. For comparison between more than two study groups; we use ANOVA (POST HOC) test. In all cases; p-value <0.05 was considered as significant.

Comparisons of proportions were performed by cross-tab using Chi-Square test when each cell has an expected frequency of five or more and the Fischer's exact test was used when one or more of cells have an expected frequency of less than 5.

The bivariate Odds Ratio (OR) and Chi-square test were used to examine unadjusted association between lifestyle related variables and serum level of Vitamin D. Moreover, a multiple logistic regression was used to investigate the effect of predicting life style factors on serum level of Vitamin D by controlling potential confounders.

Results

After analysis of the data available the following results were found (Table 1).

Serum Level of Vitamin D	Infertile		Fertile	
	N	%	N	%
Very Low	37	34.90%	13	12.50%
Low	44	41.50%	34	32.70%
Normal	20	18.90%	46	44.20%
High	5	4.7%	11	10.6%
Mean ± SD	1.93 ± 0.85		2.5 ± 0.84	

Table 1: Serum Vitamin D level among the groups under study [X^2=25.278; df=3; p=0.000].

About 75% of infertile women had very low and low serum level Vitamin D level. While about 55% of fertile women had normal or high Serum Vitamin D level 34.9% of infertile women had very low serum Vitamin D level compare to 12.5% in the fertile group and 44% of fertile women had normal Serum Vitamin D level compare to 18.9% among the infertile group. The differences between the two groups were highly significant. Regarding infertile women, the mean age was 28.8 ± 7.5. About 15% of women aged <20 years, 73.6% aged between 20-40 years and 11.3% older than 40 years. While the mean age for fertile women was 30.4 ± 7.3. About 7.7% aged less than 20 years, 80.8% aged between 20-40 years and 11.5% older than 40 years. Therefore; there is no any statistically significant deference between the two groups of study regarding different age groups (p>0.05) (Table 2).

BMI	Infertile		Fertile	
	N	%	N	%
Slim	20	18.90%	23	22.10%
Normal	46	43.40%	50	48%
Overweight	34	32.10%	29	27.90%
Obese	6	5.70%	2	1.90%
Mean ± SD	2.22 ± 0.8		2 ± 0.75	

Table 2: BMI among cases and control groups [X^2=2.754, df=3, p=0.10].

The majority of women in both groups had normal; overweight and slim while low percentage of them where obese and the differences between cases and control groups were statistically not significant (Table 3).

SE	Infertile		Fertile	
	%	N	%	N
Low	17	16%	10	9.60%
Mid	50	47.20%	27	26%
High	39	36.80%	67	64.40%
Mean ± SD	2.2 ± 0.7		2.5 ± 0.66	

Table 3: The distribution of women among different socio-economic classes [X^2=16, df=2, p=0.000].

About 63.2% of infertile women are from low or middle socio-economic classes compare to 35.6% among the fertile group and the reverse regarding those from high SE class.

The differences between the two groups were statistically highly significant (Table 4).

Diet	Infertile		Fertile	
	N	%	N	%
Rich in Vitamin D	64.20%	68	81.70%	85
Poor in Vitamin D	35.80%	38	18.30%	19
Mean ± SD	1.35 ± 0.5		1.2 ± 0.4	

Table 4: The distribution of women in relation to the type of Diet [X^2=8.2, df=1, p=0.003].

This table shows the percentage of women eating Vitamin D rich diet was significantly higher (81.7%) in the control group (fertile) compare to the infertile group with (64.2%),while percentage of women eating Vitamin D poor diet was significantly higher in infertile women (35.8%) in comparison with (18.3%) in infertile women. There was no statistically significant differences (p=0.248) among case and control regarding the level of education; among the infertile women, (25.5%) were illiterate, (43.4%) were from primary and secondary school and (31.1%) were having higher education. Regarding the fertile women (16.3%) was illiterate, (46.2%) were from primary and secondary school and (37.5%) were having higher education (Table 5).

Serum Vitamin D Level	Non-PCOS		PCOS	
	%	N	%	N
Very Low	16	40%	21	31%
Low	14	35%	30	45.50%
Normal	9	22%	11	16.70%
High	1	2.50%	4	6.10%
Mean ± SD	1.87 ± 0.85		2.3 ± 0.9	

Table 5: Serum Vitamin D level among PCOS (Polycystic Ovary Syndrome) and non PCOS cases [X^2=2.252, df=3, p=0.333].

This table shows the effect of PCOS on serum level of Vitamin D. The percentage of women with very low Vitamin D was higher in the non PCOS group, while the percentage of those with low Serum level of Vitamin D was higher in the PCOS group, Despite that the differences were statistically not significant (Table 6).

Exposure to sunlight	Infertile		Fertile	
	%	N	%	N
Good	51.90%	55	72.10%	75
Limited	48.10%	51	27.90%	29
Mean ± SD	1.5 ± 0.5		1.3 ± 0.45	

Table 6: The distribution of case and control in relation to exposure to sunlight [X^2=9.1, df=1, p=0.002].

The percentage of women with good exposure to sunlight was significantly higher in the fertile group (72.1%) compare to the infertile one (51.9%) and the reverse was noted regarding limited exposure being 48.1% in the infertile group compare to 27.9% in the fertile group (Table 7).

Occupation	Infertile		Fertile	
	%	N	%	N
Household	61.30%	65	46.20%	48
Out door	38.70%	41	53.80%	56
Mean ± SD	1.4 ± 0.5		1.5 ± 0.5	

Table 7: The effect of occupational type on case and control [X^2=4.86, df=1, p=0.019].

This table shows distribution of infertile and fertile women regarding the type of occupation. The percentage of household women was higher among infertile women (61%) and vice-versa regarding outdoor occupation. The difference was statistically significant.

The majority of women in both groups were among the white race (87.7% of the infertile and 88.5% of the fertile) while the minority were Negro (12.3% and 11.5% respectively). The differences were statistically not significant (p=0.5).

The majority of women in both groups were using hijab or Abaya (84.9% among infertile and 91.3% among the fertile), although the number of women using Boshiya in the infertile group (15.1%) was higher than those in the fertile group (8.7%) but the difference was statistically not significant (p=0.11).

Although the percentage of women in the infertile group wearing black clothes (26.4%) was higher than those in the control group (18.3%) but the difference were not statistically significant (p=0.1) (Table 8).

Variables	Unstandardized Coefficients		Standardized Coefficients		Sig.
	B-	Std. Error	Beta	T	
Constant	27.105	4.884		5.55	0
Diet	-3.933	1.787	-0.168	-2.200	0.03
Exposure time	-3.240	1.468	-0.15	-2.206	0.03
Socio-economic	3.011	1.059	0.203	2.843	0.01
Infertile and Fertile	3.015	1.149	0.145	2.624	0.01
Color of cloths	-3.839	1.478	-0.154	-2.597	0.01

Table 8: Multiple regression analysis (Stepwise).

This table shows multiple regression analysis of factors that may predispose to Vitamin D deficiency. Five factors were significantly predicting serum level of Vitamin D. They are being infertile women, from low socio-economic status, having limited exposure to sunlight, eating diet poor in Vitamin D and using black clothes (Table 8). Although the effect of color of cloths was not statistically significant, it appears to be significant when other variables were fixed.

Discussion

Infertility can cause many problems for the couples involved, particularly the women. It is supposed that the life style could affect the fertility status of the couples [19]. Vitamin D plays a role in reproductive capacity; several investigators have demonstrated higher IVF pregnancy rates in Vitamin D replete women [20]. In this study we found that the percentage of women with low and very low serum Vitamin D was significantly higher among infertile women compare to fertile women. A study was done in Baghdad city by Omar et al. also reported a significantly lower serum Vitamin D level among women with primary infertility (35.38 ± 5.83 ng/mL) compare to the control group (49.99 ± 12.9 ng/mL) [11]. Bahar et al. in Iran were reported a higher percentage of low serum Vitamin D among infertile women compare to those with normal serum level (52.78% compare to 47.22%) [3].

Another similar finding was reported in USA by Rudick et al. who reported 58% of the infertile women underwent their first IVF cycle were Vitamin D deficient and insufficient compare to 42% were Vitamin D depleted [20]. Jason et al. at USA found that the total serum 25-OH vitamin D didn´t differ between the two studied groups (30.3 ± 9.8 ng/mL in the infertile group and 28.9 ± 8.7 ng/mL in the fertile controls (P=0.57) [21]. Alberta F et al. found that implantation, pregnancy and ongoing pregnancy rate were similar among oocyte recipient with normal, insufficient or deficient total Serum 25-OHD level [22]. From the above facts still there is a controversy about the effect of Serum vitamin D level on fertility.

Regarding the effect of Age on Serum level of Vitamin D; among fertile and infertile women we found that there was no statistically significant effect which is similar to the finding reported by the other studies which were done in Iran by Morshed et al. in Iraq by Omar et al. in USA by Rudick et al. in USA [3,11,20,21]. In our sample the higher percentage of women under study in both groups were between 20-40 years age group, this is could be explained by the fact that the majority of women in our society get married in this age group.

Regarding BMI we found that there was no significant effect of BMI on serum Vitamin D level among both groups and this finding was similar to that reported by different studies done in Iraq by Omar et al. in Iran by Morshed et al. in USA by Rudick et al. and Jason et al. in USA [3,11,20,21]. While Fabris et al. found significant effect of BMI on serum Vitamin D level among infertile women undergoes IVF [23]. Regarding the SES; we found that 63.2% of infertile women were found low and mid socio-economic class compare to 35.6% among fertile group. From this could be explained by the fact that those with low income can't offer well balanced diet which is rich in Vitamin D. Although, Behbahani and Dabbaghmanesh found no such effect [3].

The above fact supported by the finding that the percentage of infertile women who took a diet poor in Vitamin D was higher than that in the fertile group and vice-versa regarding those who took a diet rich in Vitamin D and these findings were similar to that reported by Marissa et al. [24]. Regarding the level of education we found that there was no statistically significant effect of the level of education on serum Vitamin D level and this finding was similar to that reported by several studies in different countries [3,25]. This is could be explained by the fact that the level of education has no effect on dietary habit and exposure to sunlight. We found that the there was no effect of PCOS on serum level of Vitamin D whereas a study done by Roshan et al. found that the percentage of infertile women with low Vitamin D was higher among those with PCOS [26]. This difference could be due to the difference in sample size (106 in our study compare to 314 in the second study).

As exposure to sun light is important for the synthesis of Vitamin D. It is estimated that around 5-30 minutes of sun exposure without the use sun screen twice a week between 10:00 am to 3:00 pm is enough to maintain sufficient Vitamin D level within normal level. We found that the percentage of women with good exposure to sunlight was higher among the fertile group in compare to the infertile one. The factors which could influence exposure to sunlight include occupation and it's evident in our study that the percentage of women with indoor occupation (housewives) was significantly higher among the infertile group compare to the fertile group and vice versa regarding those with outdoor activity. A similar finding was reported by Danil et al. who found that indoor worker had lower 25-(OH) Vitamin D levels compare to outdoor workers (40.6 ± 13.3 *vs.* 66.7 ± 16.7 nmol/L; p<0.0001) [27].

The other factors which could affect sunlight exposure is race. In our study there was no statistically significant difference between the infertile and fertile groups regarding the skin color and this is similar to that reported by Rudick et al. who were reported that there was no statistically significant effect of the ethnic heterogeneity on Vitamin D metabolism and its subsequent effects on IVF success. The prevalence of vitamin D deficiency and insufficiency is alarmingly high in infertile patients with p value 0.59 [20]. Whereas, Jason et al. reported a significant effect of race on serum Vitamin D level. The percentage of White women with depleted Vitamin D was 87.5% compare to 54.9% with deficient serum Vitamin D. While the percentage of African American with depleted serum vitamin D was 1% compare to 6.3% with deficient Vitamin D and this is proposed to be explained by the fact that Vitamin D production is effected by the area of the skin exposed and darker colored skin takes longer time of exposure to produce the same amount of vitamin D, whereas lighter colored skin is more susceptible to erythema [28].

The third factor affecting exposure to sunlight is the type of clothes. In our study although the percentage of those women who wear Boshiya was higher in the infertile group compare to the fertile group and this difference was statistically not significant. This factor was not studied in other researches probably because Boshiya is not used by women in other countries. There is no need to compare the findings in the table shows multiple regression analysis (stepwise) with other studies because the risk factors are already discussed above in each table. The findings in this table are confirming to what has been found in the previous tables.

Recommendations

- Serum Vitamin D level should be assessed in all infertile women at Basrah city.
- Encouragement of sunlight exposure with lifestyle changes in favor of that and Vitamin D oral supplements should be offered to all infertile women.

Conclusion

The result of the study shows that there is a deficiency or insufficiency of the vitamin D in infertile women in Basra city in south of Iraq district irrespective of age of the women, BMI, race, level of education, type and color of clothes. While SES, occupation, exposure to sun light, dietary intake and supplementation all have huge effect on serum level of Vitamin D and subsequently have effect on women's fertility. We found that life style in different aspects is associated with different level of serum vitamin D of the women planning to become pregnant. Therefore, we should consider this issue and promoting life style changes in any aspect to help infertile woman to become pregnant and there is a positive increase in the level of vitamin D after taking the supplement of vitamin D3. However, it is highly recommended to take the Vitamin D3 supplements on a regular basis to overcome its deficiency or insufficiency and its effect on fertility is added to the preventive program as a part of primary health care.

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